Pentamidine isethionate

Brand Name: Nebupent, Pentacarinat, Pentam 300

AIDSinfo
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Drug Description

Pentamidine isethionate is an aromatic, diamidine-derivative antiprotozoal agent. It is structurally and pharmacologically similar to stilbamidine. The presence of a benzenecarboximidamide (aromatic amidine, benzamidine) group is associated with pentamidine's trypanosomicidal activity, and the presence of both benzenecarboximidamide groups is necessary for this activity. [1]

HIV/AIDS-Related Uses

Pentamidine isethionate was approved by the FDA on June 15, 1989, for use in the treatment of Pneumocystic jiroveci (formerly Pneumocystis carinii) pneumonia (PCP) in AIDS patients. Although pentamidine may be administered intramuscularly or intravenously (IV) for the treatment of PCP, only the IV route is currently recommended.[2] Sulfamethoxazole-trimethoprim is considered to be the primary agent for PCP in patients who can tolerate it.[3]

Pentamidine isethionate is also available in an orally inhaled form via nebulization.[4] Aerosolized pentamidine is indicated in both primary prophylaxis (HIV infected patients with a CD4 lymphocyte count less than or equal to 200 cells/m3) and secondary prophylaxis (people who have already had at least one episode) of PCP.[5]

Non-HIV/AIDS-Related Uses

Pentamidine isethionate is indicated as secondary prophylaxis in the treatment of PCP in patients who have already had at least one episode of the illness and in immunocompromised patients.[6] Pentamidine is generally used only when patients with PCP cannot tolerate the first-line of treatment of sulfamethoxazole-trimethoprim combination.[7]

Pharmacology

Limited information is available on the pharmacokinetics of pentamidine isethionate. The antiprotozoal mechanisms of action of pentamidine isethionate have not been fully elucidated, but presumably several mechanisms are involved, with variability between the different types of protozoa. Most information on the antiprotozoal activity of aromatic diamidines such as pentamidine has been derived from studies involving trypanosomes. In vitro, pentamidine appears to be directly lethal to Pneumocystis jiroveci, although the drug only moderately inhibits glucose metabolism, protein and RNA synthesis, and intracellular amino acid transport in this organism at concentrations attainable in vivo.[8] Pentamidine may interfere with nucleotide incorporation into RNA and DNA; inhibit oxidative phosphorylation and biosynthesis of DNA, RNA, protein and phospholipid; and/or interfere with folate transformation. Pentamidine isethionate may also have antifungal activity.[9]

Gastrointestinal (GI) tract absorption of pentamidine isethionate is poor, so it must be given parenterally.[10] In an early study in PCP patients, plasma pentamidine concentrations did not vary appreciably throughout the day and did not increase with successive doses of the drug. Although plasma drug concentrations generally did not increase immediately after dose administration, if an increase did occur, it was usually within 1 hour of administration. Highest plasma drug concentrations occurred in patients with varying degrees of renal impairment. Following a single 4 mg/kg of body weight intramuscular (IM) or intravenous (IV) (given as a 2-hour infusion) dose of pentamidine isethionate in patients with both AIDS and PCP, peak plasma pentamidine concentrations averaged 209 ng/ml approximately 40 minutes after the IM dose and 612 ng/ml after IV infusion completion. Following oral inhalation of pentamidine isethionate via nebulization, bronchoalveolar lavage fluid concentrations of the drug are substantially higher (at least 5 to 10 times) than those attained following IV administration. Pentamidine appears to undergo limited absorption from the respiratory tract into systemic circulation; peak plasma concentrations appear to occur at or near completion of the inhalation administration. Systemic accumulation of pentamidine does not appear to occur during oral inhalation therapy.[11]

Pentamidine isethionate is rapidly distributed and/or bound to tissues after administration. Data

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Pharmacology (cont.)

from AIDS patients indicate that following parenteral administration of pentamidine, highest concentrations of the drug are found in the liver, followed by the kidneys, adrenals, spleen, lungs, and pancreas. (4) Peak serum concentrations after a 4 mg/kg dose administered are 0.2 to 1.4 mcg/ml after IM administration and 0.5 to 3.4 mcg/ml after IV administration (over a 1- to 2-hour infusion).[12] Pentamidine is not effective for the treatment of trypanosomiasis involving the central nervous system (CNS), leading researchers to believe that the drug penetration of the CNS is poor. Limited data from AIDS patients suggests that pentamidine may distribute into the CNS in some patients, but only in very low concentrations and after prolonged (a month or longer) therapy.[13]

Deposition of orally inhaled pentamidine shows considerable interindividual variation and appears to depend on several factors, including delivery device, particle size of aerosolized drug, dose, patient position, and nebulization efficiency. Limited data from patients with HIV infection indicate that distribution of the drug in the lungs following oral inhalation via nebulization is more uniform when the patient is in the supine, rather than sitting, position.[14]

Pentamidine isethionate is in FDA Pregnancy Category C. Adequate and well-controlled studies have not been done in pregnant women, and animal reproduction studies have not been performed to date. However, studies in rabbits have shown that systemic pentamidine was associated with an increased incidence of post-implantation losses and delayed fetal ossification.[15] The drug should be used during pregnancy only when clearly needed. Spontaneous abortion has been reported during pentamidine inhalation therapy, but a causal relationship has not been established. It is not known whether pentamidine isethionate affects fertility in humans or is distributed into milk, but it apparently crosses the placenta. Because of the potential for serious adverse reactions to pentamidine isethionate in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of treatment.[16]

Protein binding of pentamidine isethionate is high (69%), with rapid binding to tissues following administration. Plasma concentrations of the drug decline in a biphasic manner, with a first half-life of 9.1 to 13.2 hours with IM administration and 6.5 hours with IV administration, and a terminal half-life of 2 to 4 weeks. Pentamidine appears to be eliminated very slowly from tissues in which the drug principally accumulates (e.g., liver, lungs); currently available assays may be inadequate to determine a third, prolonged elimination phase. Drug half-life may be prolonged in patients with renal dysfunction, although no correlation between renal function and plasma clearance of pentamidine has been found.[17]

Little is known about the elimination of pentamidine in humans.[18] Over a 24-hour period, excretion into urine via renal elimination is estimated to be 4% to 17% of an IM dose and approximately 2.5% of an IV dose. Patients may continue to excrete decreasing amounts of the drug in urine for up to 8 weeks following discontinuation of therapy. There is no information available regarding human fecal excretion of pentamidine, but in mice, the amount excreted in feces is approximately less that in urine.[19] Limited data suggest that pentamidine is not appreciably removed by hemodialysis or peritoneal dialysis, and information on the pharmocokinetics of pentamidine isethionate after oral inhalation in patients with hepatic or renal dysfunction is not available.[20]

Little information is available on natural or acquired resistance of protozoa to pentamidine. In vitro studies with Trypanosoma and Crithidia suggest that resistance to pentamidine may result from reduced uptake of the drug by the organisms. Trypanosomes resistant to pentamidine are generally cross-resistant to other aromatic diamidine derivatives (e.g., stilbamidine).[21]

Adverse Events/Toxicity

Common adverse effects seen with use of pentamidine isethionate include diabetes mellitus or hyperglycemia, elevated liver function tests, hypoglycemia, hypotension, leukopenia or neutropenia, nephrotoxicity, and thrombocytopenia. These may need medical attention if they occur

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Adverse Events/Toxicity (cont.)

after the medication is discontinued. Less common adverse effects include anemia, cardiac arrhythmias, pancreatitis, phlebitis with intravenous injection, sterile abscess with intramuscular injection, GI effects, and unpleasant metallic taste.[22]

Drug and Food Interactions

Since nephrotoxic effects may be additive, the concurrent or sequential use of pentamidine isethionate and other drugs with similar toxic potentials, such as aminoglycosides, amphotericin B, capreomycin, colistin, cisplatin, foscarnet, methoxyflurane, polymyxin B, or vancomycin, should be closely monitored or avoided.[23] Renal function determinations, dosage reductions, and/or dosage interval adjustments may be required.[24]

Blood dyscrasia-causing medications, bone marrow depressants, and radiation therapy may increase the abnormal hematologic effects of these medications and of radiation therapy; dosage reduction may be required. Concurrent use with didanosine may increase the potential for development of pancreatitis. Intravenous erythromycin used concurrently with pentamidine isethionate may increase the potential for development of torsades de pointes (a form of ventricular tachycardia with a specific variation in the conduction of the ventricular stimulus). Concurrent use of foscarnet and pentamidine isethionate may result in severe, but reversible, hypocalcemia, hypomagnesemia, and nephrotoxicity.[25]

Contraindications

Pentamidine isethionate is contraindicated in patients with a history of hypersensitivity to pentamidine isethionate.[26]

Clinical Trials

For information on clinical trials that involve Pentamidine isethionate, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Pentamidine isethionate AND HIV Infections.

Dosing Information

Mode of Delivery: Oral (inhalation via nebulization), intramuscular (deep IM injection), or intravenous (slow infusion).[27]

Dosage Form: Pentamidine isethionate solution for inhalation containing 300 mg.[28]

Pentamidine isethionate for IM or IV injection containing 300 mg.[29]

Storage: Prior to reconstitution, pentamidine isethionate should be stored between 2 C and 8 C (36 F to 46 F) unless otherwise specified by the manufacturer.[30]

Pentamidine isethionate sterile powders for injection and for oral inhalation solution should be protected from light and stored at 15 C to 30 C (59 F to 86 F). Reconstituted solutions of the drug for injection or for oral inhalation should also be protected from light. To avoid crystallization, pentamidine isethionate should be stored between 22 C and 30 C (72 F to 86 F).[31]

Chemistry

CAS Name: Benzamidine, 4,4'-(pentamethylenedioxy)di-, bis(beta-hydroxyethanesulfonate)[32]

CAS Number: 140-64-7[33]

Molecular formula: C23-H36-N4-O10-S2[34]

C46.61%, H6.12%, N9.45%, O27.0%, S10.82%[35]

Molecular weight: 592.69[36]

Melting point: 180 C[37]

Physical Description: Pentamidine isethionate occurs as white or almost white crystals or powder. The drug is hygroscopic and may be odorless or have a slight butyric odor.[38]

Stability: Following reconstitution with sterile water for injection, pentamidine isethionate solutions for parenteral use containing 60 mg/ml to 100 mg/ml are reportedly stable for 48 hours at

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Chemistry (cont.)

room temperature. Manufacturers recommend that unused portions of reconstituted solutions should be discarded. The manufacturers state that reconstituted solutions of drug that have been further diluted in 5% dextrose injection to a concentration of 1 mg/ml or 2.5 mg/ml for IV infusion are stable for up to 24 hours at room temperature. Reconstituted solutions that have been diluted to a concentration of 1 mg/ml to 2 mg/ml in 5% dextrose or 0.9% sodium chloride injection in PVC bags are reportedly stable for 24 hours exposed to normal fluorescent light at 22 C to 26 C.[39] Reconstituted pentamidine should not be mixed with any solutions other than 5% dextrose.[40]

After reconstitution with sterile water for injection, solutions of pentamidine isethionate for oral inhalation are reportedly stable for 48 hours in the original vial when stored at room temperature and protected from light.[41]

Solubility: Pentamidine isethionate's solubility in water is about 100 mg/ml at 25 C (77 F).[42]

Pentamidine isethionate is soluble in glycerol, with solubility increasing upon warming; slightly soluble in alcohol; and insoluble in ether, acetone, chloroform, and liquid petroleum.[43]

Other Names

Diamidine[44]

Lomidine[45]

Further Reading

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Watson, J. Pneumocystis carinii: where are we now? J HIV Ther. 2002 Feb;7(1):8-12. Review. PMID: 11956498

Manufacturer Information

Pentamidine isethionate
Fujisawa Healthcare Inc
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Pentam 300
Fujisawa Healthcare Inc
Parkway Center North / 3 Parkway North
Deerfield, IL 60015-2548
(800) 727-7003

Nebupent
Fujisawa Healthcare Inc
Parkway Center North / 3 Parkway North
Deerfield, IL 60015-2548
(800) 727-7003

Pentacarinat
Rhone - Poulenc Rorer
500 Arcola Road
Collegeville, PA 19426
(800) 340-7502

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday,

For More Information (cont.)

12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help
Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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